Remarks

Claim 8 was dependent on now-canceled claim 5 and, therefore, has been amended into independent form.

The present claims are directed to a pneumococcus type 5 capsular polysaccharide that is aminated on the terminal aldehyde group and conjugates and compositions thereof, in which the ketone functions of the repeating units of the polysaccharide have been subject to reduction. The cited art provides no teaching, suggestion, motivation, or reason to subject pneumococcus type 5 capsular polysaccharide to conditions for reduction of ketone moieties before coupling the polysaccharide to a polypeptide carrier by reductive amination. The applicants were the first to discover that the chemical structure of the pneumococcus type 5 capsular polysaccharide repeating unit is modified by conventional reductive amination (specification p. 5, l. 18, *et seq.*). Without this understanding there would be no reason to reduce the ketone functions prior to reductive amination, as presently claimed. Furthermore, absent a compelling reason, the ordinary artisan would avoid introducing additional synthetic steps to avoid increased time and costs for conjugate preparation and reduced yield.

The Office Action points to the paragraph bridging pp. 107-108 of Jansson for a motivation to use borohydride reduction of the Streptococcus pneumoniae type 5 capsular polysaccharide to obtain a more stable product having similar immunological activity for use in a vaccine. But Jansson's teachings are wholly speculative, stating that it "seems possible" that reduction, which "should" stabilize the polysaccharide, "should" display similar immunological activity and, therefore, it "might" be advantageous to reduce the polysaccharide. The only type of stabilization that Jansson demonstrates is a slightly better stability against chemical treatment (*e.g.*, methylation under basic conditions). But this does not imply that the reduced polysaccharide is more stable than the native polysaccharide under conditions that would make it useful in a vaccine, as suggested by Jansson (*e.g.*, physiological or storage conditions). There is nothing in Jansson or in the art that the applicants are aware of to support Jansson's assertions concerning stability of the reduced polysaccharide for use in a vaccine.

Furthermore, it has been demonstrated that modifications of a polysaccharide chemical residue can result in modifications of the polysaccharide's immunogenicity. Pinta *et al.*. Chem. Eur. J. **15**, 9747 (2009) (attached) discusses the role of a Sug*p* residue (this is the same residue as

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the sug residue present in the native structure of the pneumococcus type 5 capsular polysaccharide) in the oligosaccharide structure of the outer core (OC) region of *Yersinia enterolitica* serotype O:3 (*Ye* O:3) in its recognition by a monoclonal antibody (2B5) specific for *Ye* O:3 (see ll. 10 *et seq.* on page 9752, first col.). The structure of the native oligosaccharide structure of *Ye* O:3 is depicted in Fig 3b and comprises a Sug*p* residue (K') whereas the modified oligosaccharide structure of *Ye* O:3 after hydrazine/KOH treatment is only modified at Sug*p* residue (K in fig 3A). The mild hydrazine treatment quantitatively reduces the Sug*p* residue to Quinovosamine N acetylated (QuipNac) as mentioned on page 9750. This minor change at Sug*p* residue led to the loss of antibody recognition, as indicated in the first paragraph of page 9752: "In contrast, mAb 2B5 did not react with up to 2 μg of the hydrazine-treated LPS." Pinta *et al.* then concludes at the end of the first paragraph of page 9752 that "the Sug*p* of the *Ye* O:3 OC is biologically important; it either forms ... the mAb 2B5 epitope or it allows the OC to take the correct 3D structure that QuipNac would prevent."

Thus, Pinta *et al.* demonstrates that one cannot predict *a priori* what a chemical modification to a polysaccharide will do to the polysaccharide's immunogenicity.

Moreover, this is borne out in the claimed Streptococcus pneumoniae type 5 capsular polysaccharide. The present specification teaches that the immunogenicity of the Streptococcus pneumoniae type 5 capsular polysaccharide is particularly sensitive to modifications of the Sug residue:

> In addition, it was discovered that conversion of the Sug compound to compound X was harmful to the immunogenicity of the polysaccharide, even though this conversion is only partial - that is to say taking place only in some of the repeating units of the polysaccharide and not in all of them.

Specification p. 7, ll. 10-15. See also tables I and II, pages 38 and 39 respectively, which show that mice that were immunized with a conjugate obtained using a pneumococcus type 5 capsular polysaccharide aminated according to the conventional reductive amination method (resulting in a polysaccharide containing compound X) (group 3 mice) had the lowest antibody titers on day 36. On the other hand, mice that were immunized with a conjugate in which the sug moiety in the repeating units were maintained intact (*i.e.*, containing the unreduced ketone unit, C=O) (group 1 mice) and those immunized with a conjugate in which the sug moieties in the repeating

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units were converted into a reduced form (CHOH) before reductive amination (group 2 mice) had similar antibody titers on day 36.

In view of the foregoing, even were one motivated to employ borohydride reduction of the Streptococcus pneumoniae type 5 capsular polysaccharide, one could not reasonably predict that the resulting reduced polysaccharide would retain its immunogenicity.

Lastly, the applicants take exception with the statement in the Office Action that "with regard to the sequence of the reduction and reductive amination steps, performing the borohydride reduction on the conjugated product after the reductive amination would produce the same ketone-reduced product as does the method in the specification without necessitating an additional fragmentation step." This is incorrect and misapprehends an aspect of the invention. The specification teaches at page 5 that "it is has now been discovered that the chemical structure of the repeating unit of the pneumococcus type 5 polysaccharide is modified after reductive amination according to the conventional method," the Sug residue being converted to "X," *inter alia*, which, as described on p. 7 of the specification, is harmful to the immunogenicity of the polysaccharide. To avoid this, the specification describes at page 7 the applicants' discovery that the conversion of the Sug residue to X can be avoided by reducing the polysaccharide before reductive amination. There is no recognition or suggestion in the art of the foregoing or, consequently, that an aminated polysaccharide free of X could be made. Accordingly, the applicants discovery, embodied in the present claims, is a surprising result substantiating the non-obviousness of the present claims.

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, he is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

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